Arq Neuropsiquiatr 2002;60(4):1042-1047

GAMMA PROBE-ASSISTED BRAIN TUMOR MICROSURGICAL RESECTION

A new technique

Osvaldo Vilela Filho[1], Omar Carneiro Filho[2]

ABSTRACT - *Objectives:* The pioneering performance of gamma probe-assisted surgery (GPAS) for brain tumors, aiming not only an improvement of tumor detection, but mainly assurance of its complete removal and the study of the usual distribution of the ^{99m}Tc-MIBI in the brain SPECT of normal individuals. *Method*: Patient's informed consent and demonstration of the tumor by the preoperative MIBI SPECT were the inclusion criteria adopted for GPAS, which was performed in one patient with a right parietal lobe metastatic tumor. The radiotracer (^{99m}Tc-MIBI) was injected in a peripheral vein 5 hours before the operation. A tumor to-normal tissue count ratio equal to or greater than 2/1 was considered indicative of tumor. MIBI SPECT was performed in five normal individuals in a pilot study. *Results*: The gamma probe greatly facilitated intraoperative tumor detection (tumor to-normal brain count ratio was 5/1) and indicated a small piece of residual tumor after what was thought to be a complete tumor removal, allowing its resection, which, otherwise, would have been left behind. Postoperative CT confirmed complete tumor resection. The MIBI SPECT in normal individuals showed an increased uptake by the hypophisis, choroid plexus, skull, scalp and salivary glands and absence of uptake by the normal brain tissue. There were no complications. *Conclusion*: GPAS proved to be, in this single case, a safe and reliable technique to improve brain tumor detection and to confirm the presence or absence of residual tumor.

KEY WORDS: radioguided surgery, gamma probe, gamma probe-assisted surgery, ^{99m}Tc-MIBI, SPECT, brain tumor, brain neoplasm.

Ressecção microcirúrgica de tumor cerebral assistida por detector gama: uma nova técnica

RESUMO - *Objetivos:* A realização pioneira de cirurgia assistida por detector gama (CADG) para tumores cerebrais, objetivando-se não apenas a identificação do tumor, mas, sobretudo, assegurar-se quanto à sua completa ressecção e estudar a distribuição usual do ^{99m}Tc-MIBI no SPECT cerebral de indivíduos normais. *Método*: O consentimento informado do paciente e a demonstração do tumor pelo SPECT pré-operatório com MIBI foram os critérios de inclusão adotados para a CADG, a qual foi realizada em um paciente com metástase para lobo parietal direito. O radiotraçador (^{99m}Tc-MIBI) foi injetado em uma veia periférica 5 horas antes da cirurgia. Uma relação $\geq$ 2/1 entre a radiação gama emitida pelo tumor e pelo tecido normal foi considerada como indicativa de presença tumoral. Em um estudo piloto, SPECT cerebral com MIBI foi realizado em cinco pacientes normais. *Resultados*: O detector gama em muito facilitou a detecção per-operatória do tumor e demonstrou a presença de um pequeno resíduo tumoral após o que se pensou tratar-se de uma completa ressecção; tal resíduo, de outro modo, não teria sido percebido, o que teria impossibilitado sua exérese. Tomografia computorizada pós-operatória confirmou a completa ressecção do tumor. O SPECT com MIBI de indivíduos normais mostrou sua captação pela hipófise, plexo coróide, crânio, couro cabeludo e glândulas salivares, mas não pelo tecido cerebral normal. Não ocorreram quaisquer complicações. *Conclusão*: A CADG mostrou-se, em nosso paciente, uma técnica segura e confiável para facilitar a identificação do tumor e para confirmar a presença ou ausência de resíduo tumoral.

PALAVRAS-CHAVE: cirurgia radioguiada, detector gama, cirurgia assistida por detector gama, ^{99m}Tc-MIBI, SPECT, tumor cerebral, neoplasia cerebral.

Until the mid-1970s, brain scintigraphy was the main diagnostic imaging technique for brain tumors. Its use for this goal, however, was almost completely abandoned after clinical introduction of computed tomography (CT) and magnetic resonance imaging (MRI)[1]. Nuclear medicine techniques, though, conti-

[1]Head, Instituto do Cérebro de Goiânia, Hospital Lúcio Rebelo. Head, Stereotactic and Functional Neurosurgery Service, and Vice-Chairman, Division of Neurosurgery, Hospital das Clínicas, Medical School, Universidade Federal de Goiás. Goiânia GO, Brazil; [2]Clinical Director, Instituto de Medicina Nuclear – IMEN, Goiânia GO, Brazil.

Received 15 August 2002. Accepted 20 August 2002.

Dr. Osvaldo Vilela Filho - Head, Instituto do Cérebro, Hospital Lúcio Rebelo - Avenida 5ª Radial, 131/302 – 74823-130 Goiânia GO - Brazil. FAX: 55 62 255-0214. E-mail: ovf@ih.com.br

nued to evolve. The constant sophistication of the gamma-cameras (with two, three and four heads, and more recently, a new device named hawkeyes) and the discovery of new radionuclides (technetium-^{99m}Tc, thallium-^{201}Tl, iodine-^{123}I and ^{125}I)[1, 2] and of their carrying molecules [antibodies against antigens found in some tumors (B72.3, anticarcinoembryonic antigen antibody), iodo-á-methyltyrosine, hexamethylpropyleneamine-oxime (HMPAO), ethyl cysteinate dimmer – ECD, hexakis-2-methoxyisobutylisonitrile (MIBI or SESTAMIBI), tetrofosmin, furifosmin, metaiodobenzylguanidine, octreotide] greatly improved the sensitivity, specificity and quality of the images produced by this method[1–10].

Successful tumor radiolocalization, however, depends on tumor depth and size, being lesions smaller than 2 cm in diameter, according to some authors, difficult to identify[11,12]. Currently, though, with the improvement of the spatial resolution of the gamma-cameras, lesions with somewhat smaller diameters (0.6 cm) can already be detected. Considering that the sensitivity and specificity of radiodetection increase by minimizing the distance between the source (radiotracer) and the detector, Martin et al.[12] developed, experimentally, a hand-held self-contained gamma detecting device, the gamma probe, for intraoperative use, enabling the surgeon to identify radioactive tissues targeted by a preadministered gamma-emitting tumor-associated radiolabeled substance (radiotracer). This technique, named by others as radioguided surgery (RGS) and by the present authors as gamma probe-assisted surgery (GPAS), was introduced into clinical practice in 1985 by Martin et al.[3,4], allowing them to promptly recognize the lesion in 28 patients harboring colorectal tumors. Using a variety of radiolabeled substances[1-10], many authors have performed GPAS to map sentinel-nodes of melanomas[13], of breast[14], vulvar[15], cervical[16], prostate[17], penile[18] and thyroid[19] cancer, and to identify breast (the radiolabeled substance may be injected intravenously[20] and within[21] or around[22] the tumor), ovarian[3], colorectal[4, 5], gastroenteropancreatic[10], parathyroid[23] and thyroid[24, 25] tumors and neuroblastomas[9], with a significant successful rate.

According to a wide review of the literature performed by the present authors (database: MEDLINE, from 1966 to 2002, and LILACS) and to those provided by Schneebaum et al.[26] and Bakalakos & Burak[27], however, GPAS has never been used for brain tumors. We hypothesized that this technique could also be applied to brain tumors to facilitate its localization, to determine the best place to perform corticotomy and, above all, to assure completeness of its removal.

In this paper, we initially conducted a pilot study to determine the distribution of the radiolabeled substance used (^{99m}Tc-MIBI) in normal individuals and, for the first time, to the best of our knowledge, applied the gamma probe to guide microsurgical resection of a brain tumor. The technique used is detailed described.

METHOD

This study was performed after approval of the Ethical Committee of Hospital Lúcio Rebelo (Goiânia, Brazil), institution where the present study is being carried out. Inclusion criteria for this study included: 1- informed consent of the patient and closest relative and 2- accumulation of the radiotracer in the brain tumor as shown by the preoperative SPECT (single photon emission computed tomography).

Radiotracer - The radiotracer used was the ^{99m}Tc-MIBI (DuPont Pharmaceuticals Co, USA), administered intravenously in a dose of 30 mCi. This radiotracer was initially developed for imaging myocardial perfusion[7]. During such studies, Muller et al., cited by Vallabhajosula[6], first observed, in 1987, that ^{99m}Tc-MIBI accumulates in lung tumors. Subsequently, a number of investigators reported the potential of ^{99m}Tc-MIBI to image parathyroid adenomas, osteosarcoma, and tumors of the brain, breast, lung and thyroid[6].

^{99m}Tc-MIBI is a lipophilic, cationic substance, which enters the cells of any tissue through a passive diffusion mechanism (electrochemical gradient) and binds mainly to the mitochondrias, greatly influenced by their negative charges and by their increased density in tumors. Adequate blood flow must be present for uptake to occur. Dead cells do not accumulate ^{99m}Tc-MIBI. Besides the transient bitter taste claimed by some patients, there seems to be no other side effects or contraindications for its use. The normal pattern of the MIBI SPECT includes some uptake by the skull, facial bones, salivary glands, pituitary gland and choroid plexus; however, there is no uptake by the normal brain tissue, which looks "cold". Usually, the greater the metabolic activity and tumor aggressiveness, the greater is the uptake[2, 6-8].

Preoperative SPECT - After the diagnosis of a brain tumor by CT and/or MRI, a SPECT is performed. The patient is placed supine in the bed of a room sound-isolated beside the gamma-camera suite and encouraged to stay very relaxed. The eyes and ears of the patient are blocked to prevent increased cerebral blood flow to the visual and auditory areas. A tourniquet is applied to the head just above the ears (it is kept in place for about 15 minutes) to prevent increased blood flow to the scalp and skull, just like in the way the SPECT is used as a diagnostic tool for brain death. Only then 30 mCi of ^{99m}Tc-MIBI is injected in a peripheral vein. The patient is taken to the SPECT (Dual Head Gamma-camera Vertex, ADAC Laboratories, USA) suite and the exam is performed through the acquisition of 64 bidimensional images which are reconstructed (butterworth filter) tomographicaly in 3D, obtaining 6-

mm thick axial, coronal and sagittal slices. The encephalic distribution of the ^{99m}Tc-MIBI is then evaluated. To achieve a good resolution image of the tumor, when processing the images in the screen, one should remove the background and increase the window. This simple maneuver significantly improves visualization of the tumor, considering that accumulation of the ^{99m}Tc-MIBI by the tumor is not always as intense as desired.

Gamma probe - The hand-held gamma probe (Europrobe model CE 0459 (Fig 1); Eurorad, Strasbourg, France) is a cylinder with 11.5 cm in length and 1 cm in diameter, with a knee 1.5 cm away from its tip, which contains a highly sensitive cadmium telluride crystal solid-state radiation detector. The probe detects gamma-rays exclusively from structures just in front of its extremity, like a unidirectional microphone and relays it through a preamplifier and a signal processor. The system works as a gamma-camera, but instead of producing images, it provides both an audible signal and a digital display of radioactive counts. Counting rates are obtained from brain areas distant from the tumor and, after its exposure, also from the tumor. A tumor to-normal brain count ratio equal to or greater than 2/1 was indicative of tumor tissue, as proposed by other authors[3, 9] for tumors of other organs.

Surgical Technique - Five hours before the operation, while the patient is still in the ward, 30 mCi of ^{99m}Tc-MIBI is administered intravenously, following the protocol already described for the preoperative SPECT (blockage of ears and eyes and placement of the head tourniquet). Once the brain has been exposed, the gamma probe is used to determine the counting rate of brain tissues distant from the expected tumor location and the best area to perform the corticotomy (the area closest to the tumor, where the highest counting rate of gamma-rays is obtained, respecting eloquent areas), which is usually carried out through a sulcus deprived of important vascular structures. After meticulous microdissection, the tumor is identified (at this point, the gamma probe is applied to establish the tumor counting rate), and resected. Once gross total tumor removal is thought to have been accomplished, the gamma probe is again employed to assure completeness of resection: theoretically, in the absence of residual tumor, tumor to-surrounding brain count ratio should be lesser than 2/1.

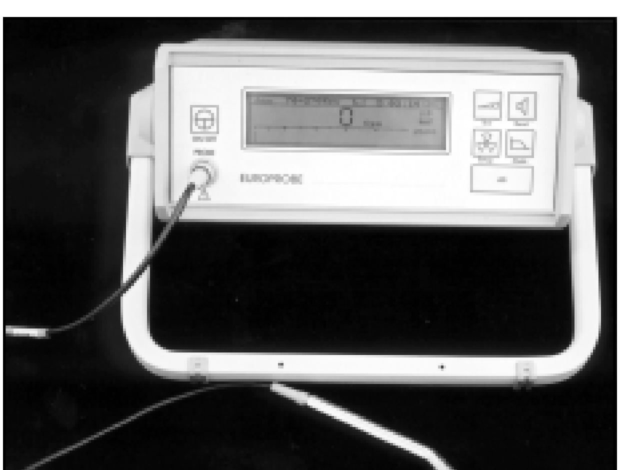

Fig 1. The gamma probe system - Europrobe (Eurorad, Strasbourg, France).

Patients

a. Pilot study: In order to achieve a better comprehension of ^{99m}Tc-MIBI distribution in the brain, to avoid misinterpretation of the results of MIBI SPECT in patients presenting with brain tumor and to compare the data obtained with our equipment with those obtained by other authors[2], after informed consent we performed this procedure in five patients, without any neurological complaints, who underwent myocardial perfusion imaging. The study was performed following the same protocol above mentioned in all but one patient (the head tourniquet was not applied).

b. Index-patient (case report): A 62-year-old male patient presented with severe headache for 20 days, following a fall of his own height and a consequent mild head injury. The neurological evaluation revealed right ataxia, unsteadiness and papilledema. Past history inquiry revealed high blood pressure, arrhythmia, and a right kidney carcinoma, operated (nephrectomy) two years before admission to our Service. Neither chemotherapy nor radiotherapy was performed. Both CT and MRI showed two lesions, one in the right cerebelar hemisphere and another in the right parietal lobe (Fig 2-A. and Fig 2-B.), suggestive of brain metastases. High gastrointestinal endoscopy, whole body bone scintiscan and ultrasound of the abdomen and pelvis were normal. Chest x-ray evidenced an asymptomatic mass in the inferior lobe of the right lung. A stereotactic biopsy of both intracranial lesions confirmed the suspicion of metastases from renal cell carcinoma. Since the posterior fossa lesion was the one threatening the patient's life, we decided for its removal, which was accomplished completely and without complications. Postoperatively, however, the patient remained with complaints of increased intracranial pressure. The postoperative CT confirmed complete removal of the cerebelar lesion. The brain SPECT with ^{99m}Tc-MIBI (Fig 2-C.) also showed the parietal mass and nothing in the posterior fossa. Eight days after the first operation, continuing the manifestations of high intracranial pressure, the patient underwent gamma probe-assisted microsurgical resection of the right parietal lobe. The tumor to-normal brain count ratio was 5/1. After what was thought to be a complete tumor resection, the gamma probe detected a residual small piece of tumor (3 mm in diameter) in the posterosuperior quadrant of the tumor bed, which could only be seen after a complete repositioning of the microscope. After its removal, the counting rate of the tumor bed and surroundings was practically equal to the normal brain tissue. The postoperative course was uneventful. There were no

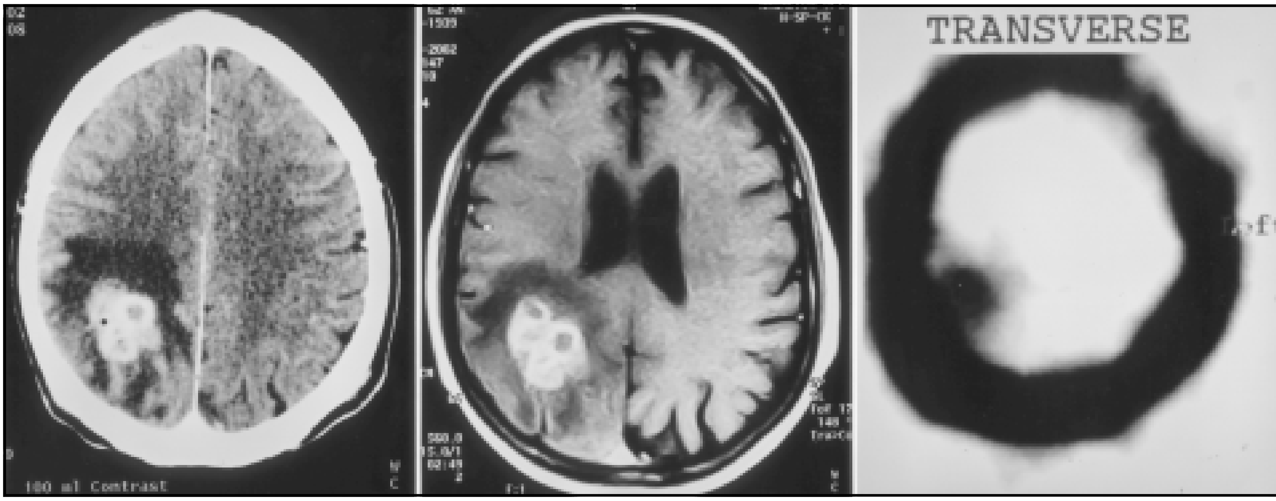

Fig 2. Preoperative CT (A), MRI (B) and ^{99m}Tc-MIBI SPECT (C) showing a metastasis from a renal carcinoma in the right parietal lobe of our index-patient.

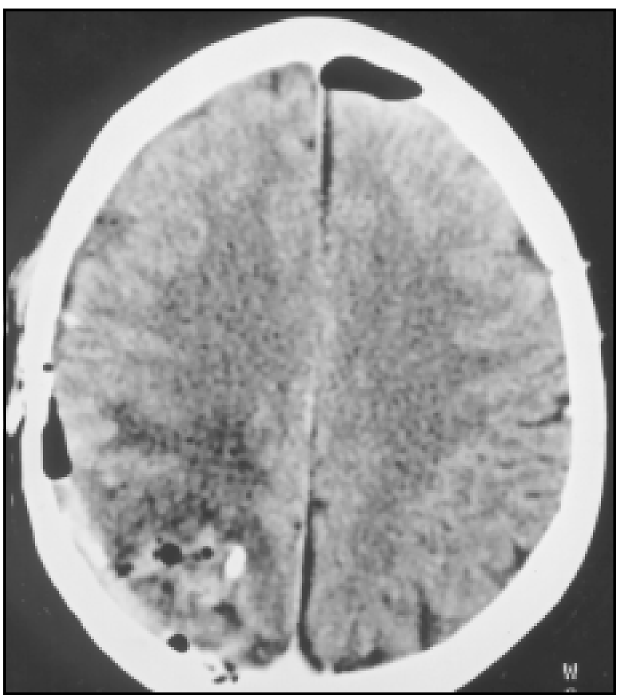

Fig 3. Postoperative CT showing complete resection of the right parietal lobe tumor of our index-patient using the gamma probe-assisted surgery (GPAS).

complications. The anatomopathologic study of the tumor after both operations confirmed the results of the stereotactic biopsy. The postoperative CT showed no residual brain lesion (Fig 3). The patient was discharged in the tenth postoperative day. So far, after a follow-up of three months, there has been no evidence of brain tumor recurrence.

RESULTS

The MIBI SPECT of the control subjects showed uptake of the radiotracer by the pituitary gland, choroid plexus, parotid and other salivary glands and by the scalp and skull, which was decreased but not abolished by the tourniquet applied to the head; on the other hand, there was no uptake by the brain.

The gamma probe enabled us to completely remove the right parietal lobe tumor of our index-patient, which, in this specific case, would not have been possible without its assistance. It also contributed for the rather quick detection of the subcortical lesion and to establish the shortest route for its approach.

DISCUSSION

Gamma probe-assisted surgery (GPAS) or radioguided surgery (RGS), enabled by the development of the gamma probe[12], was clinically introduced by Martin et al.[4], in 1985, in an attempt to facilitate intraoperative tumor detection and its complete removal. The principle of the procedure is quite logical: a substance, known for its affinity to a particular tumor, is labeled with a gamma-emitting radionuclide and injected in the patient, usually intravenously, some time before the operation. The ideal time for its administration depends basically on the half-life of the radiotracer used. During the operation the tumor is identified as the area with the highest counting rate detected by the gamma probe. The counting rate of the surrounding normal tissue is also recorded, allowing the determination of tumor to-normal tissue count ratio, which is considered indicative of tumor tissue when equal to or greater than 2/1[3,9]. After tumor resection, absence of residual tumor is indicated by a count ratio inferior to 2/1.

The gamma-probe is resistant, portable, not too expensive and easy to use, presenting a high sensitivity and specificity, as demonstrated by the GPAS performed to remove a wide variety of tumors[3-5,9,10,20-25] and sentinel-nodes[13-19]. In fact, its sensitivity seems to be greater than that of CT (Bell et al.[3]: 11 of 13 patients harboring ovarian cancer underwent preoperative CT-scan, which was normal in all of them), MRI (Martinez et al.[23]: one out of three patients with parathyroid disease underwent preoperative MRI and CT, being both normal) and external scintigraphy (Martin et al.[4]: this procedure was normal in 11 out of 23 patients with colorectal tumor).

We the present authors, were the first to employ the gamma probe to assist a brain tumor microsurgical resection. The technique proved to be very valuable, prompting detecting the tumor region, and thus indicating the closest route to the lesion; but even more important, it enabled the detection of a residual part of the tumor (3-mm in diameter) and its removal, which, otherwise, would have been left behind. We stated before that the gamma probe provides both an audible signal and a digital display of radioactive counts. Although in our patient we relied basically on the digital display of the radioactive counts, we also observed a significant increase of the audible signal when the gamma probe detected both the main core of the tumor and its residual part. To make this resource even more useful, one could proceed like Martinez et al.[23]. These authors eliminated (squelched) the sound of the background radioactivity in normal tissues; being the sound squelched, the criterion for the signal processor to produce a perceptible sound is a level of radioactivity significantly above background. It is our intention to adopt a similar strategy in our next patients.

The results of the pilot study, performed before this pioneering procedure and designed to determine the usual pattern of distribution of the radiotracer in the brain SPECT of normal subjects, were quite similar to those reported by López-Amor[2]. The uptake of the ^{99m}Tc-MIBI by the pituitary gland and choroid plexus and the absence of uptake by the normal brain could be explained, respectively, by the absence and presence of an active blood-brain barrier in these areas[2]. In this author's experience, such pattern of radiotracer's uptake makes the interpretation of the MIBI SPECT in fact easier, and not more difficult, as could be expected[2].

In our protocol, we defined as an inclusion criterion the appearance of the tumor in the preoperative SPECT. However, other authors, using GPAS for tumors of other organs, demonstrated that the gamma probe could detect the tumor even when external scintigraphy was negative (11 out of 23 cases)[4]. Considering this report, it is our plan to start performing GPAS irrespective the findings of the preoperative SPECT. The reason we elected the ^{99m}Tc-MIBI instead of the ^{201}Tl chloride as the radiotracer for this research was the better quality of images produced by the former[2], probably due to the higher photon flux that it produces, allowing a greater amount of statistical certainty in image reconstruction[8]. Besides, in a research going on in our Service concerning the differential uptake of different radiotracers by distinct types of brain tumors, the ^{99m}Tc-MIBI SPECT showed some tumors not detected by the ^{201}Tl SPECT, as in the case of a patient with a recurrent grade II fibrillary astrocytoma of the right temporal lobe (unpublished data).

One should consider the ideal timing for the intravenous injection of the ^{99m}Tc-MIBI (or any other radiotracer), what can be of utmost importance. Martinez et al.[23] used this radiotracer for GPAS in three patients with hyperparathyroidism. Two patients were operated 2-4 hours after the injection of the radiotracer, and one patient, 6 hours after it; the latter was the unique patient in whom the gamma probe failed to detect the adenoma. These findings suggest that the operation should be performed before the 6-hour half-life of ^{99m}Tc, as we did in our patient.

Other important issue is the safety of the technique for both the patient and the surgical team. Using a dose of 30 mCi of ^{99m}Tc-MIBI, the radiation absorbed by the patient is very low[7], being approximately equivalent to that of a chest x-ray. As to the surgical team, considering the radiation absorbed by other organs, since the brain was not included in these studies[7], the degree of exposition is well below the dose limits recommended by the International Commission of Radiological Protection.

Thanks to the directions provided by Prof. Dr. Ronald Tasker, who pointed that sort of an old-fashioned radioguided surgery for brain tumors had been performed in the 1950s, we were able to find an old paper from Morley & Jefferson[28] in this regard. One should remember that, by that time, ventriculography and angiography were the gold-standard studies for imaging the central nervous system. Besides, microsurgery was still not available and stereotactic surgery had only been recently introduced into clinical practice. Considering all these limitations, Morley & Jefferson[28], in an attempt to improve tumor detection, first "marked" the tumor with ^{32}P (intravenous injection), a pure beta-emitter with high affinity for brain tumors (the range of its beta particles in the white matter is only 5 to 8 mm) and then inserted a modified Geiger-Muller probe counter (it picks up the beta particles emitted by the tumor cells containing ^{32}P) through the brain parenchyma into the expected location of the tumor. They used this technique for two main purposes: mapping the tumor extent, after brain exposure, performing multiple insertions of the 2 to 3 mm in external diameter probe through the brain, undoubtedly a risky procedure, and pin-pointing the tumor location to guide its biopsy through a burr-hole. The authors commented about the advantage of an accurate definition of the absolute tumor boundaries using radioactivity detection as a means to achieve complete tumor resection, and regretted that this would call for a degree of sensitivity far beyond the one the apparatus they used could provide. A similar technique was used by other authors at that time and even later by others[29, 30].

In spite of the refinements of modern neuroradiology, it is well established, based on anatomopathologic studies, that cells from tumors like gliomas extend beyond the margins seen both on CT and MRI[31, 32]. So, it is improbable that even with the use of the neuronavigator or of the intraoperative CT or MRI these cells could be detected. GPAS, however, brings a new hope to change this scenario. Since Bell et al.[3] were able to disclose even a microscopic ovarian cancer, one could speculate about its usefulness to detect the tumor cells present beyond the margins of a brain tumor. And if that is the case, one could even foresee the possibility to completely remove high-grade gliomas localized in regions away from eloquent brain areas, like those of the non-dominant frontal and temporal polar regions. Although GPAS may facilitate tumor localization and thus guide the best place to perform the corticotomy, we have no doubt that its main application in neurosurgery will be the intraoperative detection of residual tumor (macro or even microscopic tumors) after its apparently complete removal, for which goal the technique and tools here reported are apparently adequate, we feel tempted to say. Obviously, much more cases will be necessary to confirm or contradict our supposition.

Acknowledgements - The authors are thankful to Ronald Tasker, MD, for his advice, to Herbert Almeida O. e Souza, MD, and Rogério Damasceno, MD, for their support, and to Suzana Oellers, for proofreading this manuscript.

REFERENCES

1. Van Heertum RL, Tikofsky RS. Brain tumors, other diseases, and activation. In Van Heertum RL, Tikofsky RS (Eds.). Functional cerebral SPECT and PET imaging. 3. Ed. Philadelphia: Lippincott Williams & Wilkins, 2000:275-277.
2. López-Amor MF. Patología tumoral. In Carreras JL, Sopena R, Llamas JM, Caballero E (Eds.). Aplicaciones clínicas de la SPECT cerebral. Barcelona: Masson, 1994:67-75.
3. Bell J, Mojzisik C, Hinkle G Jr, Derman H, Schlom J, Martin E. Intraoperative radioimmunodetection of ovarian cancer using monoclonal antibody B72.3 and a portable gamma-detecting probe. Obstet Gynecol 1990;76:607-611.
4. Martin DT, Hinkle GH, Tuttle S, et al. Intraoperative radioimmunodetection of colorectal tumor with a hand-held radiation detector. Am J Surg 1985;150:672-675.
5. Kuhn JA, Corbisiero RM, Buras RR, et al. Intraoperative gamma detection probe with presurgical antibody imaging in colon cancer. Arch Surg 1991;126:1398-1403.
6. Vallabhajosula S. Radiopharmaceuticals in oncology. In Khalkhali I, Maublant JC, Goldsmith SJ (Eds.). Nuclear oncology: diagnosis and therapy. Philadelphia: Lippincott Williams & Wilkins, 2001:31-62.
7. Wackers FJT, Berman DS, Maddahi J, et al. Technetium-99m hexakis 2-methoxyisobutyl isonitrile: human biodistribution, dosimetry, safety, and preliminary comparison to thalium-201 for myocardial perfusion imaging. J Nucl Med 1989;30:301-311.
8 Waxman AD. Thallium-201 and technetium-99m methoxyisobutyl isonitrile (MIBI) in nuclear oncology. In Sandler MP, Coleman RE, Wackers FJT, Patton JA, Gottschalk A, Hoffer PB (Eds.). Diagnostic nuclear medicine. 3.Ed. Baltimore: Williams & Wilkins, 1996:1261-1274.
9. Martelli H, Ricard M, Larroquet M, et al. Intraoperative localization of neuroblastoma in children with ^{123}I- or ^{125}I-radiolabeled metaiodobenzylguanidine. Surgery 1998;123:51-57.
10. Schirmer WJ, O'Dorisio TM, Schirmer TP, Mojzisik CM, Hinkle GH, Martin EW. Intraoperative localization of neuroendocrine tumors with 125I-TYR (3)-octreotide and a hand-held gamma-detecting probe. Surgery 1993;114:745-752.
11. Van Nagell JR Jr, Kim E, Casper S, et al. Radioimmunodetection of primary and metastatic ovarian cancer using radiolabeled antibodies to carcinoembryonic antigen. Cancer Res 1980;40:502-506.
12. Martin DT, Aitken D, Thurston M, et al. Successful experimental use of a self-contained gamma detecting device. Curr Surg 1984;41:193-194.
13. Alex JC, Weaver DL, Fairbank JT, Rankin BS, Krag DN. Gamma-probe-guided lymph node localization in malignant melanoma. Surg Oncol 1993;2:303-308.
14. Tanis PJ, Deurloo EE, Valdes Olmos RA, et al. Single intralesional tracer dose for radio-guided excision of clinically occult breast cancer and sentinel node. Ann Surg Oncol 2001;8:850-855.
15. De Cicco C, Sideri M, Bartolomei M, et al. Sentinel node biopsy in early vulvar cancer. Br J Cancer 2000;82:295-299.
16. Verheijen RH, Pijpers R, van Diest PJ, Burger CW, Buist MR, Kenemans P. Sentinel node detection in cervical cancer. Obstet Gynecol 2000;96:135-138.
17. Wawroschek F, Vogt H, Weckermann D, Wagner T, Hamm M, Harzmann R. Radioisotope guided pelvic lymph node dissection for prostate cancer. J Urol 2001; 166: 1715-1719.
18. Wawroschek F, Vogt H, Bachter D, Weckermann D, Hamm M, Harzmann R. First experience with gamma probe guided sentinel lymph node surgery in penile cancer. Urol Res 2000;28:246-249.
19. Lippi F, Capezzone M, Miccoli P, et al. Use of surgical gamma probe for the detection of lymph node metastases in differentiated thyroid cancer. Tumori 2000;86:367-369.
20. Cox CE, Hyacinthe M, Berman C, Dupont EL, Wagner A. Localization of an occult primary breast cancer with technetium-99m sestamibi scan and an intraoperative gamma probe. Cancer Control 1996;3:448-450.
21. Gennari R, Galimberti V, De Cicco C, et al. Use of technetium-99m-labeled colloid albumin for preoperative and intraoperative localization of nonpalpable breast lesions. J Am Coll Surg 2000;190:692-698.
22. Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surg Oncol 1993;2:335-340.
23. Martinez DA, King DR, Romshe C, et al. Intraoperative identification of parathyroid gland pathology: a new approach. J Pediatr Surg 1995;30:1306-1309.
24. Boz A, Arici C, Gungor F, Yildiz A, Colak T, Karayalcin B. Gamma probe-guided resection and scanning with TC-99m MIBI of a local recurrence of follicular thyroid carcinoma. Clin Nucl Med 2001;26: 820-822.
25. Barbet J, Peltier P, Bardet S, et al. Radioimmunodetection of medullary thyroid carcinoma using indium-111 bivalent hapten and anti-CEA x anti-DTPA-indium bispecific antibody. J Nucl Med 1998;39:1172-1178.
26. Schneebaum S, Even-Sapir E, Cohen M, et al. Clinical applications of gamma-detection probes – radioguided surgery. Eur J Nucl Med 1999;26:S26-35.
27. Bakalakos EA, Burak WE Jr. The radioimmunoguided surgery (RIGS) system as a diagnostic tool. Surg Oncol Clin N Am 1999;8:129-144.
28. Morley TP, Jefferson G. Use of radioactive phosphorus in mapping brain tumours at operation. Br Med J 1952;ii:4784-4787.
29. Desiatnikov VM, Kotliarov EV, Liass FM. Apparat dlia lokalizatsii novoobrazovanii golovnogo mozgo vo bremia operatsii s pomoshch' ih P32 [An instrument for localization of brain neoplasms during surgery with the use of P32]. Med Radiol (Mosk) 1968;13:41-44.
30. Konovalov AN. Die intraoperative diagnostic von Gliomen des Grosshirns [Intraoperative diagnosis of cerebral gliomas]. Zbl Neurochir 1980;41:43-48.
31. Burger PC, Dubois PJ, Schold SC, et al. Computerized tomographic and pathologic studies on the untreated, quiescent, and recurrent glioblastoma multiforme. J Neurosurg 1983;58:159-169.
32. Kelly PJ, Daumas-Duport C, Kispert DB, Kall BA, Scheithauer BW, Illig JJ. Imaging-based stereotaxic serial biopsies in untreated intracranial glial neoplasms. J Neurosurg 1987;66:865-874.